Drug safety in pregnancy - monitoring congenital anomalies

Morgan, Margery; De Jong-Van Den Berg, Lolkje T. W.; Jordan, Sue

Published in:
Journal of Nursing Management

DOI:
10.1111/j.1365-2834.2011.01250.x

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2011

Drug safety in pregnancy – monitoring congenital anomalies

MARGERY MORGAN DM, FRCOG[1], LOLKJE T.W. DE JONG-VAN DEN BERG PHARM D, PhD[2] and SUE JORDAN MB, Bch, PhD, PGCE (PE) and FHEA[3]

[1]Lead Clinician for CARIS, *Singleton Hospital, AMBU Health Board, Swansea, UK*, [2]Professor in Pharmacoepidemiology, *Department of PharmacoEpidemiology and PharmacoEconomics, Division of Pharmacy, University of Groningen, The Netherlands and* [3]Reader, *College of Human and Health Sciences, Swansea University, Swansea, UK*

Correspondence
Margery Morgan
CARIS – the Congenital Anomaly and Register Information Service for Wales
Singleton Hospital
Swansea
UK
E-mail:
margery.morgan@wales.nhs.uk

For the EUROmediCAT Steering Group. Members of the EUROmediCAT Steering Group: Helen Dolk, Maria Loane and Marlene Sinclair, University of Ulster, UK; Marian Bakker, University Medical Center, Groningen, The Netherlands; Corinne de Vries, University of Bath, UK; Ester Garne, Lillebaelt Hospital Kolding, Denmark; Anna Latos Bielenski, University, Poznan, Poland; Sue Jordan, Swansea University, UK; Anna Pierini, Consiglio Nazionale della Richerche, Italy; Joan Morris, Wolfson Institute of Preventive Medicine, London, UK; Awi Wiesel, University of Mainz, Germany.

MORGAN M., DE JONG-VAN DEN BERG L.T.W. & JORDAN S. (2011) *Journal of Nursing Management* **19**, 305–310

Drug safety in pregnancy – monitoring congenital anomalies

Aim This paper outlines research into the causes of congenital anomalies, and introduces a pan-European study. The potential roles of nurses and midwives in this area are illustrated by a case report.
Background Since the thalidomide disaster, use of drugs in pregnancy has been carefully monitored to prevent anything similar happening again. However, monitoring is incomplete and questions remain unanswered.
Key issues Many medicines are essential for the health of pregnant women. However, drug use in pregnancy requires surveillance. Methods include spontaneous reporting of adverse events, cohort studies and case control studies. It is hoped that a Europe-wide study, combining data from several congenital anomaly registers, will provide a sufficiently large population to assess the impact of selected drugs on congenital anomalies. However, this work depends on the consistency of reporting by nurses and midwives.
Conclusion Drug safety in pregnancy remains undetermined. Collaboration across Europe has the potential to provide a framework for safety evaluation.
Implications for nursing management Prescribers should consider the possibility of pregnancy in women of child-bearing age. Careful review of maternal drug use in early pregnancy is essential. Midwives and nurses should be aware of adverse event drug reporting systems, including congenital anomaly registers.

Keywords: congenital anomalies, nurses and midwives, research methods

Accepted for publication: 3 February 2011

Background

Drugs can affect the growing fetus at any time during pregnancy. The period of greatest risk for congenital anomalies is the first trimester (3 months) of pregnancy, which is the time of organ development. As women may not realize they are pregnant for some time into the first trimester, prescribers must be cautious when prescribing for all women of childbearing age and men trying to father a child (British National Formulary 2010).

Thalidomide was prescribed in the late 1950s for pregnant women suffering with morning sickness and was also available as an over-the-counter drug in some countries. Unfortunately, during the following years

DOI: 10.1111/j.1365-2834.2011.01250.x

many children were born with congenital anomalies, particularly phocomelia, a limb reduction defect. The National Congenital Anomalies System was set up in England and Wales in 1964 to provide surveillance of all congenital anomalies born and be in a position to prevent a similar disaster. Drug companies from then on had to comply with stricter reproductive toxicity testing.

Currently, drugs are tested in the reproductive period by animal studies only. As a result, the chances of predicting a problem with the developing human fetus is limited. Pregnant women, understandably, are excluded from drug trials.

Knowing the pharmacology and toxicology of thalidomide did not predict the resulting anomalies so, unfortunately, these adverse effects may only be discovered after a drug has been used in human pregnancy (Mitchell 2003).

The question in early pregnancy that prescribers (including non-medical prescribers) ask is: Is this drug really necessary? If there is any doubt then most clinicians would not prescribe. However, for women with chronic diseases such as diabetes, epilepsy and asthma, continuing medication is necessary for maintaining maternal health and hence fetal wellbeing. Other women may be on long-term treatment for depression or anxiety or require regular analgesia. Pre-conception counselling is important to avoid exposing the developing fetus to drugs without a safety track record in pregnancy. It is also an opportunity to prescribe folic acid, particularly the increased dose for diabetics and epileptics to reduce the risk of neural tube defects in the fetus (British National Formulary 2010).

Drugs in pregnancy

The most widely used publication for advice on drugs in pregnancy in the United Kingdom is the British National Formulary (BNF). Recently, the format has changed. The pregnancy advice has been taken from the appendices and is now with each individual drug. The research evidence for the effects of drugs on mother and baby is reviewed elsewhere (Jordan 2010).

Pregnancy, childbirth, breastfeeding and developing infants may be affected by medicines or environmental exposure. The impact of medication on the fetus may include congenital anomalies, prematurity, low birth weight and developmental delay. As the ova of female infants are formed before birth, there is potential for prenatal exposures to affect subsequent generations.

Manufacturers of many drugs and herbal remedies advise against use in pregnancy and lactation on the grounds that there are insufficient human data to demonstrate safety. No drugs have been subjected to randomized controlled clinical trials for teratogenicity in human pregnancy. Therefore, no drug has been demonstrated as 'safe'. The evidence for transgenerational adverse drug reactions is largely derived from case reports of incidental exposure, observation studies, usually based on databases from Scandinavian countries, and animal studies.

Relatively few drugs are known to cause congenital anomalies, but only drugs that have been used for many years in thousands of women with no evidence of harm can be designated 'generally regarded as safe'. In reality, no drugs always harm the developing fetus all the time. Estimates vary as to the incidence of congenital malformations: up to 30% with warfarin, up to 16% with sodium valproate (Aronson 2006). Drugs associated with anomalies include:

- Warfarin (used to prevent venous thrombosis) – can cause the fatal warfarin syndrome, which includes nasal hypoplasia, eye defects, heart problems, limb shortening, deafness, scoliosis and seizures.
- Isotretinoin (treatment for severe acne) – can cause defects that include hydrocephalus, blindness, facial problems, cleft palate, deafness, heart defects and spina bifida.
- Valproic acid (anti epileptic drug) – can cause neural tube defects, cardiac defects, facial problems, renal problems, limb, skull and muscle defects.
- Drugs acting on the renin–angiotensin system, prescribed for hypertension or heart failure (Appendix 1).

The importance of this work is illustrated by the case described in Appendix 1. This case emphasizes the importance of good communication facilitating an accurate drug history. In the UK this is usually taken by the midwife early in pregnancy.

Drug safety studies

At present there are three approaches to identifying the risks of drugs in pregnancy. These are outlined below.

Spontaneous adverse event reporting

Events are reported voluntarily but their validity is compromised by an unknown denominator number (the total number of women taking the drug in early pregnancy). This reporting of cases can act as a very useful early warning sign, particularly where there is a high risk of a specific anomaly. Anomalies can be reported

by all health-care professionals. Where available, the local congenital anomaly register should be alerted to any such anomalies, suspected or confirmed. However, spontaneous reporting relies on the cooperation of busy clinicians. In addition, when reports are made, up to a year after birth, the mother may have forgotten what medicines she was receiving during early pregnancy. Therefore, a thorough drug history in early pregnancy is very important: this will be available for review if a congenital anomaly occurs.

Cohort studies

These studies follow women taking a certain drug and record the pregnancy outcome compared with a group not taking the drug. Follow up of both groups is essential. A disadvantage here is that for a drug to detect a moderate or low risk of causing an anomaly a large cohort is necessary. Obstetricians specializing in medical disorders of pregnancy may maintain detailed records of all affected pregnant women in their area. The processes and outcomes of care can then be analysed and compared with outcomes for the population as a whole. However, even over 10–20 years, there will be too few cases of congenital anomalies in medium-sized hospitals for any useful statistical testing. Also, from our experience, not all women take this opportunity to receive specialist care: the women most at risk – those least motivated to take care during pregnancy – do not regularly attend consultants' clinics. This is particularly important for conditions such as diabetes, where poor glycaemic control in the mother can have serious adverse effects on the pregnancy and fetus.

Case–control studies

These review cases of pregnancies where a baby is born with a specific congenital anomaly and compare them with controls in terms of medication usage. Controls can be normally formed births or births with other anomalies. Case–control studies have more statistical power to detect moderate to low risk of anomalies than cohort studies. An example of such a study is described as follows.

EUROmediCAT – a European approach to drug safety in pregnancy

The European Surveillance of Congenital Anomalies (EUROCAT, http://www.eurocat-network.eu) is a network of population-based congenital anomaly registers covering nearly one-third of all births in 20 European countries (Figure 1). This amounts to 1.5 million births per year. Started in 1979, EUROCAT was developed to provide epidemiological surveillance of all congenital anomalies. In recent years drug information has been enhanced on the central register enabling, for example, investigations on antiepileptic drugs and their risks (Dolk *et al.* 2008, Jentink *et al.* 2010a,b). For many European countries only certain areas are covered by EUROCAT. Whole population coverage is achieved in Scandinavian countries, and Wales. This is a very important consideration for statisticians interpreting the data.

The EUROmediCAT study aims to build a European system to check the safety of drugs in pregnancy. It will provide a system for informing risk–benefit profiles of medicines in relation to congenital anomalies to a much fuller extent. The central aim is to build a European system for reproductive safety evaluation that enables us to identify systematically and comprehensively the possible adverse effects in pregnancy of a drug in humans at the earliest stage post-marketing, and to monitor and evaluate safety measures undertaken in Europe. The specific objectives are:

- To develop and test an efficient system for safety evaluation of drugs during pregnancy, based on the EUROCAT network of congenital anomaly registers combined with existing population-based databases with information on drugs prescribed.
- To assess the risk of congenital anomaly in all drugs with particular emphasis on certain groups of drugs:
    - Anti-epileptic drugs (particularly newer drugs, e.g. lamotrigine).
    - Insulin analogues (because the safety of long-acting analogues is not established).
    - Anti-asthmatic drugs (there is increased usage as asthma increases in the population.
    - Anti-depressant drugs (possible link to cardiac anomalies in the baby with selective serotonin reuptake inhibitors).

These drugs have been selected because they are commonly prescribed to young women and case reports and small cohort studies have engendered concern over use in pregnancy. Only a large dataset will be able to provide an assessment of impact.

- To evaluate the efficacy of pregnancy-related drug safety measures, including pregnancy-prevention programmes. These are in place for thalidomide (used in myeloma), isotretinoin (acne) and acitretin

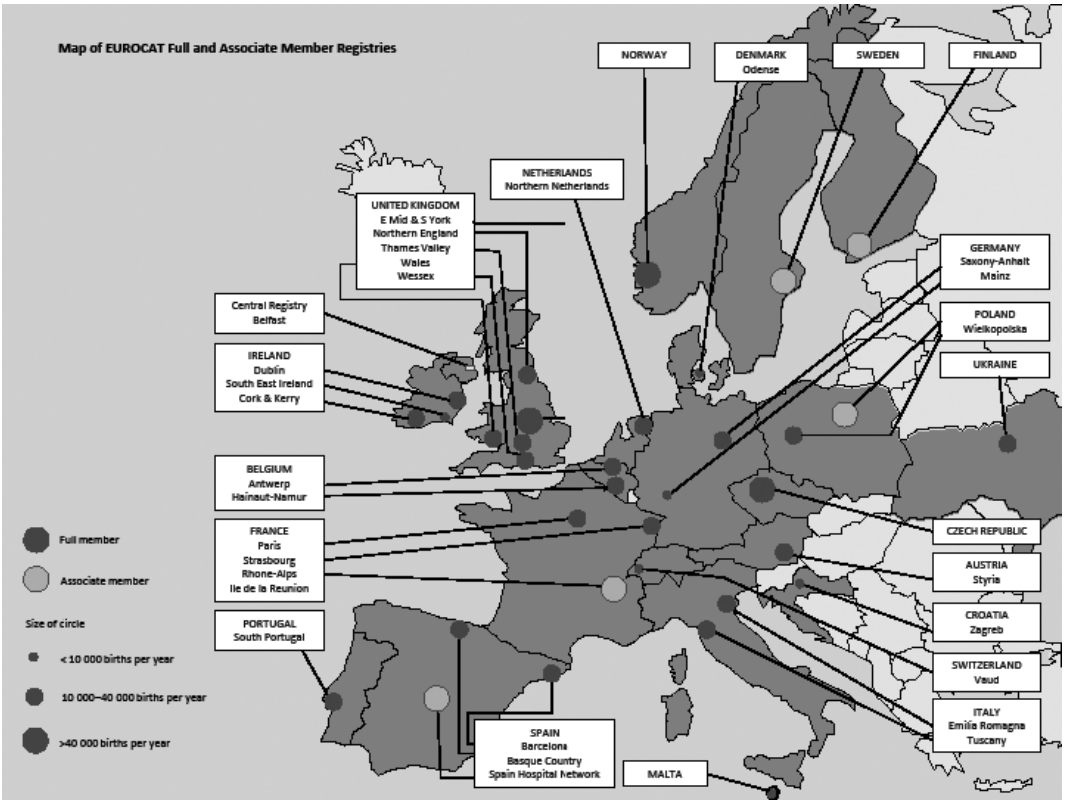

Figure 1
EUROCAT congenital anomaly registers.

(psoriasis). Pregnancy-prevention programmes apply to drugs known to have a teratogenic effect on the developing fetus. The instructions accompanying these drugs state clearly the need to prevent pregnancy and the time to wait after ceasing drug treatment before attempting a pregnancy. Women are instructed to perform regular pregnancy testing and are recommended to use the safest contraceptive techniques.

We propose to interrogate our databases to identify any instances of pregnancy among women prescribed these drugs, and the use of prescribed contraceptives among these women. The study will also evaluate internet access by pregnant women to drugs and safety information about drugs.

Data is supplied by the individual congenital anomaly registers to the EUROCAT central database, which has strict data quality. The data is obtained from various sources: birth registers, inpatient data, midwives, paediatric nurses, obstetricians and paediatricians reporting to congenital anomaly registers. Uniquely, EUROmediCAT will analyse this data in association with information on prescriptions issued in pregnancy to affected and unaffected women. Researchers will work only with anonymized data. The study is due to start in the spring of 2011 and run for 4 years.

Limitations

Work on databases is limited by failure of spontaneous reporting and incomplete population coverage, for example in the UK. The UK cannot participate in EUROmediCAT as a whole, as the area is not completely covered by a congenital anomaly register. The National Congenital Anomaly System set up after the thalidomide disaster in England and Wales has recently ceased providing surveillance. At present Wales is the only register suitable to participate. The Congenital Anomaly Register and Information Service for Wales (CARIS) is a multiple source reporting congenital anomaly register with coverage of all babies with congenital anomalies born to mothers normally resident in Wales (CARIS 2010). The register includes terminations of pregnancy and spontaneous fatal losses. It records maternal details including drug usage and health issues. In England only 50% of births occur in areas with established congenital anomaly registers. Most of these registers do not record maternal drug usage. East Anglia, London and the South East do

not have a register. In Scotland, congenital anomaly data is derived from routine data systems and provided by the Information Services Division, National Health Service (NHS) Services, Scotland. Northern Ireland has no congenital anomaly register.

The causes of most congenital anomalies remain unknown, and it may not be possible to obtain information on all putative influences. For example, some work has implicated landfill sites (Palmer *et al.* 2005), and information on such exposure is not always available or would require extensive meteorological or hydrological data to determine exposure. Whether collected by spontaneous reports or hospital records, certain information may be poorly recorded. For example, maternal reporting, may seriously underestimate the incidence of use of amphetamines, opiates and cocaine (Burns *et al.* 2006), making it difficult to assess the impact of these possible alternative causes of anomalies (Rasmussen & Frías 2008). Resource limitations also mean that not all drugs can be considered within any single project.

Conclusion

The evaluation of drug safety in pregnancy remains a challenge. This new study involving collaboration of congenital anomaly registers in Europe will facilitate closer scrutiny of adverse effects of drugs taken in pregnancy. Meanwhile, health-care professionals should reflect on their role in medicines management for women of child-bearing age.

Implications for nurse and midwife managers

Constant vigilance is essential when discussing medications with any woman who could be pregnant or considering pregnancy, as the case study in Appendix 1 illustrates. Policies and procedures are needed to ensure that:

- Prescribers (including non-medical prescribers) ascertain the date of last menstrual period and, if appropriate, discuss the possibility of pregnancy before any new medicine is prescribed and remind women of the importance of pre-conception counselling when issuing repeat prescriptions.
- Midwives listing drugs currently administered during the initial booking of the pregnancy appointment ensure that appropriate checks are undertaken (Appendix 1).
- All health-care practitioners report congenital anomalies to the appropriate national or regional registers at the earliest possible opportunity. If data are incomplete, it will be impossible to establish the causes of congenital anomalies. Adverse reactions including congenital anomalies thought to be due to a drug should be reported using the UK yellow card system (MHRA 2010).

Acknowledgements

Marsham Moselhi and Mrs R kindly gave their permission for publishing the case report.

References

Aronson J.K. (2006) *Meyler's Side Effects of Drugs: the International Encyclopedia of Adverse Drug Reactions and Interactions*, Elsevier, New York, NY.

British National Formulary (2010) *British National Formulary No. 60*. British Medical Association and the Pharmaceutical Society of Great Britain, London.

Burns L., Mattick R.P. & Cooke M. (2006) The use of record linkage to examine illicit drug use in pregnancy. *Addiction* **101** (6), 873–882.

CARIS (2010) CARIS, the congenital anomaly register and information service for wales. Available at: http://www.wales.nhs.uk/caris, accessed 21 January 2011].

Chow K.M. & Lam C.M. (2004) Angiotensin II receptor antagonist in pregnancy. *Journal of Perinatology* **24**, 56–57.

Cooper W.O., Hernandez-Diaz S., Arbogast P.G. *et al.* (2006) Major congenital anomalies after first trimester exposure to ACE-inhibitors. *New England Journal of Medicine* **354**, 2443–2451.

Dolk H., Jentink J., Loane M.A. *et al.* (2008) Does lamotrigine use in pregnancy increase orofacial cleft risk relative to other malformations? *Neurology* **71**, 714–722.

Jentink J., Loane M.A., Dolk H. *et al.* (2010a) Valproic acid monotherapy in pregnancy and major congenital malformations. *New England Journal of Medicine* **362**, 2185–2193.

Jentink J., Dolk H., Loane M.A. *et al.* (2010b) Intrauterine carbamazepine exposure and specific congenital malformations: systematic review and case-control study. *BMJ* **341**, c6581. doi:10.1136/bmj.c6581.

Jordan S. (2010) *Pharmacology for Midwives: The Evidence Base for Safe Practice*, 2nd edn. Palgrave Macmillan, Basingstoke.

MHRA (2010) Medicines and healthcare products regulatory agency. Available at: http://www.yellowcard.gov.uk, accessed 25 January 2011.

Mitchell A.A. (2003) Systematic identification of drugs that cause birth defects – a new opportunity. *New England Journal of Medicine* **349** (26), 2556–2559.

NICE (2008) National Institute for Health and Clinical Excellence, Diabetes in Pregnancy clinical guideline 63, published by NICE, London, Available at: www.nice.org.uk, accessed 30th March 2011.

Palmer S.R., Dunstan F.D., Fielder H., Fone D.L., Higgs G. & Senior M.L. (2005) Risk of congenital anomalies after the opening of landfill sites. *Environmental Health Perspectives* **113** (10), 1362–1365.

Rasmussen S.A. & Frías J.L. (2008) Non-genetic risk factors for gastroschisis. *American Journal of Medical Genetics Part C: Seminars in Medical Genetics* **148C** (3m), 199–212.

Appendix 1

Case study

Mrs R was a 30-year-old Asian woman with very little English. She was expecting her third child, having had two healthy babies in 2002 and 2004. Since the last pregnancy she had developed hypertension, treated by her general practitioner (GP) with olmesartan (angiotensin II receptor antagonist). This was recorded by the midwife at a booking visit done with an interpreter at 11 weeks gestation. The aspirin she was taking for migraines was stopped by her GP following this. She continued taking olmesartan. At 20 weeks the anomaly scan of the baby showed a reduced amount of amniotic fluid. A repeat scan, 2 weeks later, showed the appearance of no fluid at all. The kidneys were thought to be normal but the bladder difficult to outline. This suggested a problem with renal function. After further scans at the tertiary centre the parents decided to terminate the pregnancy because of the poor prognosis in terms of pulmonary hypoplasia (lung development is compromised by reduced amniotic fluid). This was at 26 weeks gestation.

While inducing labour following feticide it was noticed Mrs R was taking her own supply of olmesartan. This was brought to the attention of her team who were surprised by this. The drug is contraindicated in pregnancy and its effects could have caused the renal problems of the baby. Unfortunately, the parents declined a post-mortem to confirm this.

Olmesartan

Olmesartan is an antihypertensive drug of the angiotensin II receptor antagonist group. The British National Formulary (2010) advises to avoid prescribing in pregnancy because of adverse effects on fatal blood pressure control and renal function. It can also cause oligohydramnios (reduced amniotic fluid) and possible skull defects.

Case reports have shown renal failure in babies where the mother has taken drugs in this group beyond 20 weeks gestation. Stopping the drug in the first trimester gives an improved outcome but the advice remains to avoid angiotensin II receptor antagonists at any time in pregnancy (Chow & Lam 2004, Cooper *et al.* 2006).

Implications for practice

Several senior health professionals missed the importance of the drug history as she was recorded as not taking any drugs in one section of the notes and the drug itself was recorded in a different section concerning medications. Language difficulties may have played a part in this.

Counselling before conception is recommended for all diabetic mothers (Diabetes in Pregnancy, NICE Guideline 2008) and may have been useful here and for all mothers taking medications to consider changes in therapy in pregnancy.

